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Guidance for Industry

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CAPRINES

DRAFT GUIDANCE

This guidance is intended to standardize and simplify methods used in the evaluation of new anthelmintics submitted for approval to the European Union, Japan, and the United States.

This guidance represents the agency's current thinking on the efficacy of anthelmintics concerning caprine products regulated by the Center of Veterinary Medicine, FDA. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulation, or both.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 99N-[insert number when assigned].

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EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR CAPRINES

Recommended for Consultation
at Step 4 of the VICH Process
in February 1999
(written procedure)
by the VICH Steering Committee

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Endorsed by the VICH Steering Committee at Step 3 of the VICH Process

In February 1999 by written procedure

INTRODUCTION

These guidances for caprines were developed by the Working Group established by the Veterinary International Co-operation on Harmonization (VICH), Anthelmintic Guidances. They should be read in conjunction with the VICH Efficacy of Anthelmintics: General Recommendations (EAGR) which should be referred to for discussion of broad aspects for providing pivotal data to demonstrate product anthelmintic effectiveness. The present document is structured similarly to the EAGR with the aim of simplicity for readers comparing both documents.

The guidances for caprines are part of this EAGR and the aim is (1) to be more specific for certain specific issues for caprines not discussed in the overall guidances; (2) to highlight differences with the EAGR on efficacy data recommendations and (3) to give explanations for disparities with the EAGR.

It is also important to note that technical procedures to be followed in the studies are not the aim of this guidance. We recommend to the sponsors to refer to the pertinent procedures described in details in other published documents e.g.WAAVP Second Edition of Guidances for Evaluating the Efficacy of Anthelmintics in Ruminants (Bovine, Ovine, Caprine) Veterinary Parasitology ***58***: 181-213, 1995.

Since caprines are considered a minor species, the cost of a full development program may preclude the development of products for this species, and since the helminth species of caprines are identical to those of ovines, it is recommended that consideration be given to an abbreviated schedule of studies to obtain approval.

A. General Elements

1 - The evaluation of effectiveness data

Only controlled tests based on parasite counts of adults/larvae are recommended both for the dose determination and dose confirmation studies, since critical tests generally are not considered to be reliable for ruminants. Egg counts/larval identification is the preferred method to evaluate the effectiveness in field studies. Long-acting or sustained-release products should be subjected to the same evaluation procedures as other therapeutic anthelmintics. Adequate parasite infection should be defined in the protocol according to regional prevalence or historic and/or statistical data.

2 - Use of natural or induced infections

Dose determination studies generally should be conducted using induced infections with either laboratory or recent field isolates.

Dose confirmation studies should be conducted using naturally infected animals which can have superimposed induced infections of certain parasites that will not interfere with the resident intestinal population. This procedure will allow a wide range of parasites. For claims against hypobiotic larvae, only natural infections should be considered. Sponsors should aim for a maximum period of accumulation of hypobiotic larvae for the particular parasite species being targeted in trial animals. This will be area or regionally dependent. Specific details on area or regional situations should be obtained from experts on a case by case basis. In all cases animals need to be housed (to preclude reinfection) for a minimum of 1 week before treatment.

Persistent efficacy studies should be conducted using induced infections with recent field isolates.

The history of the parasites used in the induced infection studies should be included in the final report.

3 - Number of infective parasitic forms recommended for induced infections.

The number to be used is approximate and will depend on the isolate that is used. The final number of larvae used in the infection should be included in the final report. Table 1 shows the range of numbers recommended.

Table 1 - Number of infective stages used to produce adequate infections in goats for anthelmintic evaluation

Parasites	VICH
Abomasum	
Haemonchus contortus	400 – 4,000
Teladorsagia circumcincta	6,000 – 10,000
Trichostrongylus axei	3,000 – 6,000
Intestines	
Cooperia curticei	3,000 – 6,000
T. colubriformis & T. vitrinus	3,000 – 6,000
Nematodirus spp.	3,000 – 6,000
Oesophagostomum spp.	500 – 1,000
Chabertia ovina	800 – 1,000
Bunostomum trigonocephalum	500 – 1,000
Strongyloides papillosus	80,000
Gaigeria pachyscelis	400
Trichuris spp.	1,000
Lungs	
Dictyocaulus filaria	1,000 – 2,000
Liver	
Fasciola hepatica (metacercaria)	100 - 200 (chronic) 1,000 – 1,500 (acute)

4 - Recommendations for the calculation of effectiveness

4.1. Criteria to grant a claim

To be granted a claim the following pivotal data should be included:

a) Two dose confirmation studies conducted with a minimum of six adequately infected non-medicated animals (control group) and six adequately infected medicated animals (treated group);

b) The differences in parasite counts between treated and control animals should be statistically significant ($p<0.05$);

c) Effectiveness should be 90% or higher calculated using transformed (geometric means) data.

d) The infection of the animals in the study will be deemed adequate based on historical, parasitological and/or statistical criteria.

This effectiveness standard (= 90% or higher) is based on helminth removal from the host. If, however, the focus of regional anthelmintic treatment is to target prevention of pasture contamination due to the epizootology of gastrointestinal helminth parasites, then a higher minimum efficacy standard may be applied. Sponsors should discuss such situations with the regulatory authorities prior to commencement of trial work.

4.2 Number of animals (dose determination, dose confirmation and persistency trials)

The minimum number of animals used per experimental group is a critical point. Although the number of animals will depend on the possibility to process the data statistically according to adequate statistical analysis, it has been recommended, to achieve harmonization, that the inclusion of at least six animals in each experimental group is a minimum.

In cases where there are several studies none of which have six adequately infected animals in the control group (for example, important rare parasites), the results obtained could be pooled to accumulate 12 animals in the studies; and statistical significance calculated. If the difference are significant ($p<0.05$), effectiveness may be calculated and if the infection is deemed adequate, the claim may be granted. Sampling techniques and estimation of worm burden should be similar among laboratories involved in the studies to allow adequate and meaningful extrapolation of the results to the population.

4.3 Adequacy of infection

Concerning minimum adequate number of helminths, the decision will be made when the final report is submitted based on statistical and historical data, literature review, or expert testimony. The range of caprine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Generally the minimal mean number of nematodes considered to be adequate is 100. Lower mean counts are to be expected with *Bunostomum* spp, *Oesophagostomum* spp., *Trichuris* spp., and *Dictyocaulus* spp. For *Fasciola* spp., minimal mean counts of 20 adults is considered adequate.

4.4 Label claims

Adult or L4 parasites: The term immature on the labelling is not acceptable. For adult claims as a general rule the treatment should not be administered earlier than 21 to 25 days after infection; optimum for most species is 28 to 32 days. Major exceptions are *Oesophagostomum* spp. (34 to 49 days), *Bunostomum* spp. (52 to 56 days), *Strongyloides papillosus* (14 to 16 days) and *Fasciola* spp.(8 to 12 weeks).

For L4 claims, treatments should be given as a general rule 7 days after infection with the following exceptions: 3 to 4 days for *Strongyloides papillosus,* 5 to 6 days for *Haemonchus* spp*.,* *Trichostrongylus* spp. and *Cooperia* spp*.*, 8 to 10 days for *Nematodirus* spp. and 15 to 17 days for *Oesophagostomum* spp*.* For early immature *Fasciola* spp., treatments should be given 1 to 4 weeks after infection and for late immatures at 6 to 8 weeks.

5. Treatment procedures

5.1 - The method of administration (oral, parenteral, topical, slow-release etc.), formulation and extent of activity of a product will influence the protocol design. It is advisable to consider the weather and animal relationship with regard to effectiveness of topical formulations. Slow-release products should be tested over the entire proposed effective time unless additional information suggests that this is unnecessary. e.g. blood levels demonstrate steady state at all point**s** of the proposed therapeutic period.

5.2 - Treatment Route. When the drug is to be administered in the water or in a premix, it should be done as much as possible following the labelling recommendations. Palatability studies may be required for medicated premixes. Samples of medicated water or feed should be collected to confirm drug concentration. The amount of medicated product provided to each animal should be recorded to ensure that the treatment satisfies the label recommendations. For products used topically, the impact of weather (e.g. rainfall, UV light)**,** and coat length impact should be included in the evaluation of the effectiveness of the product.

6 - Animal selection, allocation and handling

Test animals should be clinically healthy and representative of the age, sex, and class for which the claim of the test anthelmintic is to be made. In general the animals should be ruminating, and older than 3 months of age. Animals should be assigned randomly to each treatment. Blocking in replicates by weight, sex, age, and/or exposure to parasites may aid in reducing trial variance. Faecal egg/larval counts are also useful to allocate the experimental animals.

For induced infections the use of helminth naive animals is recommended. Animals not raised in a helminth-free environment should be treated with an approved anthelmintic drug to remove pre-existing infections followed by faecal examination to determine that the animals are helminth free.

Good husbandry practices should be followed and the animals should be vaccinated according to local practices. This information should be provided in the final report. A minimum seven-day acclimatisation period is recommended. Housing and feed-water should be adequate according to the geographical location. Animals should be monitored daily to determine adverse reactions.

B. Specific evaluation studies

1 - Dose Determination Studies

A dose determination trial and/or sheep/goat comparative pharmacokinetic studies where appropriate, should verify if the dose selected is effective in goats.

2 - Dose Confirmation Studies

At least two dose confirmation studies including at least the dose limiting helminth(s) and stages in each study are recommended. If efficacy is demonstrated for the test parasites a claim can be supported for all the helminth species claimed for the sheep host. For additional descriptions of the procedures refer to EAGR.

3 - Field Efficacy Studies

4 - Persistent Efficacy Studies

Two basic study designs have been used to pursue persistent efficacy claims. One using a single challenge, another using multiple daily challenges following treatment. For consistency of interpretation of results a standardised study design is recommended using multiple daily challenges, as this most closely mimics what occurs in nature.

Two trials (with worm counts) are recommended for a persistent efficacy claim (for each duration and helminth claim) each with a non-treated and one or more treated groups. At least six animals in the control group should be adequately infected. Persistent efficacy claims should only be granted on a species-by-species basis.

In the protocol using multiple daily challenges, different groups of animals are treated and exposed to a daily natural or induced challenge for 7, 14, 21 or more days after the treatment, then at approximately three weeks after the last challenge (or earlier) the animals are examined for parasite burden.

Persistent efficacy claims should be supported by a minimum 90% effectiveness based on geometric means.